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HYDROLYSIS AND PHOTOLYSIS OF PAROXETINE, A SELECTIVE SEROTONIN REUPTAKE INHIBITOR, IN AQUEOUS SOLUTIONS

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Abstract—The hydrolysis and photolysis of paroxetine HCl, a selective serotonin reuptake inhibitor, in aqueous buffer solutions (pH 5, 7, and 9), in synthetic humic water, and in lake water were investigated at 25°C in the dark and in a growth chamber outfitted with fluorescent lamps simulating the ultraviolet (UV) output of sunlight. Paroxetine was degraded completely within 4 d by simulated sunlight in all aqueous media. Photolysis of paroxetine HCl was accelerated by increasing pH. The $t_{1/2}$ values at pH 5, 7, and 9 were 15.79, 13.11, and 11.35 h, respectively. The half-lives of paroxetine in synthetic humic water and two lake waters were slightly longer than in pH 7 buffer. Two photoproducts were detected and their structures were identified by liquid chromatography-mass spectrometry in positive mode. Photoproduct I was found to be photolytically unstable, being gradually degraded after 12 to 18 h of irradiation. However, photoproduct II was photolytically very stable throughout the experiment period, indicating that it was persistent to further photodegradation. In the dark, paroxetine in all aqueous solutions was found to be stable over a 30-d period. In conclusion, paroxetine is a relatively photolabile drug that has a possibility of photodegradation by sunlight in surface water.

Keywords—Hydrolysis Photolysis Paroxetine Serotonin reuptake inhibitor Photoproducts

INTRODUCTION

Selective serotonin reuptake inhibitors are among the most heavily prescribed drugs in the United States and have been shown to induce spawning in mussels at trace aqueous concentrations [1]. Due to their heavy usage, detectable concentrations of these drugs and their metabolites/degradation products may be expected in wastewater treatment effluent released into water bodies and drinking water sources and the persistence of them or their degradation products may cause adverse impacts on aquatic organisms.

Paroxetine hydrochloride (CAS: 61869-08-7) is one of several selective serotonin reuptake inhibitors currently used in the treatment of clinical depression, obsessive-compulsive disorder, and panic disorder. In a survey performed by NDCHealth (Atlanta, GA, USA) in 2002, paroxetine was one of the top 200 prescriptions for 2002 by number of U. S. prescriptions dispensed (http://www.rxlist.com/top200.htm). Mainly paroxetine is oxidized to an unstable catecol followed by further methylation and the major metabolite is conjugated rapidly to glucuronide and sulfate ethers in animals and humans [2,3]. This major metabolite has not been found to inhibit serotonin reuptake significantly. Paroxetine and its metabolites in human plasma [4–7], in human serum [8,9], and in tablets [10,11] have been quantified by high-performance liquid chromatography (HPLC) or by gas chromatography. Recently, it was reported that a paroxetine metabolite was detected in surface water in 139 streams across 30 states in the United States during 1999 and 2000 [12]. In forced degradation studies, paroxetine was relatively stable under acid, base, and heat [9]. However, exposure to hydrogen peroxide and light under wet conditions caused paroxetine to degrade to various products [9].

Chemicals that cannot absorb light above 290 nm are resistant to direct photodegradation; however, there are many oxidants and reductants capable of accelerating photodegradation in the environment. Examples of such oxidants are hydroxyl radical, singlet oxygen, carbonate radical, humic acid, and fulvic acid [13–24].

The purpose of this investigation was to measure the potential for paroxetine to be degraded by photolysis and hydrolysis, to identify degradation products, and to estimate the importance of hydrolysis and photolysis to the fate of paroxetine in aquatic environments including buffer solutions, synthetic humic water, and lake waters.

MATERIALS AND METHODS

Chemicals

Paroxetine-HCl was extracted with methanol and purified by recrystalization with *n*-hexane from Paxil® (GlaxoSmithKline, Research Triangle Park, NC, USA). Its purity and identity were confirmed by HPLC and liquid chromatography-mass spectrometry. The mass spectrum showed an exact $[M+H]^+$ of *m/z* (mass/charge) 310. Standard buffer solutions used to calibrate the pH meter electrode and all salts used to prepare buffer solutions were reagent grade or better and obtained from Fisher Scientific (Pittsburgh, PA, USA). All solvents were HPLC grade and were obtained from Fisher Scientific. Humic acid (sodium salt) was obtained from Aldrich (Milwaukee, WI, USA). Deionized water was used to prepare the buffer solutions.

Preparation of paroxetine HCl standard solution, buffer solutions, and synthetic humic water

Paroxetine HCl standard stock solution was made up in methanol at a concentration of 1,000 mg/L. Three aqueous buffer solutions were prepared. Buffer at pH 5 (sodium acetate buffer) consisted of 300 ml of 0.01 M sodium acetate and 200

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ml of 0.01 M CH_3COOH. Buffer at pH 7 (sodium phosphate buffer) consisted of 250 ml of 0.01 M Na_2HPO_4 and 340 ml of 0.01 M NaH_2PO_4. Buffer at pH 9 (sodium borate buffer) consisted of 900 ml of 0.01 M H_3BO_3 and 400 ml of 0.01 M NaOH. Synthetic humic water was made according to U.S. Environmental Protection Agency (U.S. EPA) Guidelines [25]. In short, 20 g of the humic acid was extracted with 1 L of 0.1% NaOH solution by stirring for 1 h at room temperature. The resulting mixtures were centrifuged and then filtered through a 0.45 μm microfilter. The pH was adjusted to 7.0 with dilute H_2SO_4 and filter-sterilized through a 0.2-μm microfilter. Two microfilters were used to remove any microorganisms, because this was an abitic experiment. Preaging was accomplished by exposing to sunlight. Before use it was diluted 10-fold with 0.01 M phosphate buffer to produce a pH 7.0 mixture with an absorbance of 5.00×10^{-2} au at 370 nm. Also two lake waters were collected from Mississippi State University (Mississippi State, MS, USA) and Chocktaw Lake (Ackerman, MS, USA) and filtered using 0.2-μm filter and then stored in a refrigerator at 4°C. The pH and absorbance values at 370 nm were 7.60 and 7.25 and 3.50×10^{-2} au and 2.00×10^{-2} au, respectively.

Photolysis and hydrolysis experiments

Photolysis and hydrolysis experiments were conducted in each pH 5, 7, and 9 buffer solution, synthetic humic water, and two lake waters at a concentration of 5 mg/L. For photolysis, a 0.5 ml of aliquot of the stock solution was added to 100 ml of each buffer solution, synthetic humic water, and two lake waters. Thus, the final test solutions were 0.5% methanol. Samples were prepared in 2-ml, capped clear borosilicate glass vials and irradiated in a temperature-controlled growth chamber outfitted with fluorescent lamps (Light Sources FL40T12-/BL, Milford, MA, USA) simulating the UV output of sunlight at 25°C. These lamps did not emit wavelengths below 290 nm. These lamps have been used in other experiment and their spectral output is reported in this published work [22]. The light intensity was measured before starting an experiment and two times a week over the experimental period using an EPP2000 Miniature Fiber Optic Spectrometer and SpectraWiz (Ver 2.1) software (StellarNet, Tampa, FL, USA). Control samples (hydrolysis samples), having the same initial concentration as photolysis samples, were kept in the dark at the same temperature. Samples were withdrawn to analyze the amounts remaining in solutions at 0, 1, 3, 7, 12, 18, 24, 36, 48, 72, and 168 h (for buffer solutions) and 0, 1, 2, 4, 8, 16, 24, 48, and 72 h (for synthetic humic water and two lake waters) of treatment. In order to identify whether the degradation of photoproducts is by photolysis or by hydrolysis, 12-h photodegraded samples were prepared and incubated for 10 d in the dark. Experiments were carried out in duplicate. The rate constants were calculated by linear regression analysis of a plot of the natural logarithm (Ln C/Co) of residual paroxetine concentration versus time, where Co is the initial concentration and C is the concentration at a certain time. The quantum yield was calculated by the following equation:

$$\Phi = \frac{k_{290\text{-}400}}{\sum I_\lambda \varepsilon_\lambda}$$

where Φ is the quantum yield, k is the degradation rate constant, I_λ is the irradiance, and ε_λ is the molar absorptivity. Because it was polychromatic radiation, $\Sigma I_\lambda \varepsilon_\lambda$ was calculated as sum of $I_\lambda \cdot \varepsilon_\lambda$ at each wavelength from 290 to 400 nm.

UV/vis spectrophotometer and HPLC analysis

The UV/vis absorption spectrum of paroxetine was recorded with a Model 8453 UV/Vis spectrophotometer (Hewlett-Packard, Waldbronn, Germany). The test solutions were the unirradiated mixtures at pH 5, 7, and 9, which were 1×10^{-5} M paroxetine. The amount of paroxetine remaining in solution was measured by direct injection of the sample onto a Waters 2695 HPLC with UV detection using a Waters (Model 996, Milford, MA, USA) photodiode-array detector at wavelength of 235 nm. Data were processed using MassLynx (Ver 3.4) software (Waters). The degradation products were separated from the parent compound using a Waters Spherisorb® 5 μm C8 (4.6 × 150 mm) analytical column. The mobile phase used was composed of acetonitrile-distilled water containing 10 mM aqueous triethylamine (60:40, v/v), with the pH adjusted to 4.8 by addition of 85% phosphoric acid. The flow rate was 1.0 ml/min. For each solution, the amount of paroxetine remaining was calculated as a percentage of concentration prior to incubation (zero time). The amount of degradation products generated was calculated as a percentage of peak area for the parent compound as standards for degradation products were not available.

LC-ESI-MS analyses

Liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) in positive mode was performed on a Micromass quattro micro mass spectrometer (Micromass UK, Manchester, UK), operating at a capillary voltage of 3 kV, cone voltage of 40 kV, source temperature of 80°C, cone temperature of 240°C, cone gas flow 60 L/h, and desolvation gas flow 609 L/h. The entire column eluents of samples exposed to light for 24 h were directly introduced into the mass spectrometer through the ESI interface. The MS scan range was *m/z* 90 to 400. Degradation products were separated on a Phenomenex Luna 5-μm phenyl-hexyl (250 × 2 mm; Torrance, CA, USA) column. Elution was carried out with acetonitrile (A) and 10 mM aqueous ammonium acetate (B). The solvent gradient began at A:B (10:90, v/v) for 2 min and proceeded to A:B (90:10, v/v) over 30 min. The flow rate was 0.2 ml/min.

RESULTS AND DISCUSSION

UV spectrum of paroxetine

Paroxetine showed a maximum absorbance (λ_{max}) at 293 nm in all buffer solutions (Fig. 1). No significant differences were observed in UV spectra measured at pH 5, 7, or 9. Spectral data indicated that paroxetine absorbed light at wavelengths above 290 nm and should be susceptible to photodegradation.

Degradation kinetics

In hydrolysis experiments, paroxetine was found to be stable in all pH buffer solutions for 30 d. Lambropoulos et al. [10] also have reported that paroxetine was stable for 6 d at room temperature when protected from light in mobile phase (10 mM 1-decane sulfonic acid sodium salt and 10 mM sodium phosphate monobasic in water [pH 3.0]-acetonitrile [60:40, v/v]). However, exposed to simulated sunlight, paroxetine was degraded completely within 4 d. Photolysis of paroxetine was accelerated by increasing pH, but did not show a wide difference between buffers (Fig. 2). The $t_{1/2}$ values and rate constants at pH 5, 7, and 9 were 15.79 ± 0.36, 13.11 ± 0.39, and

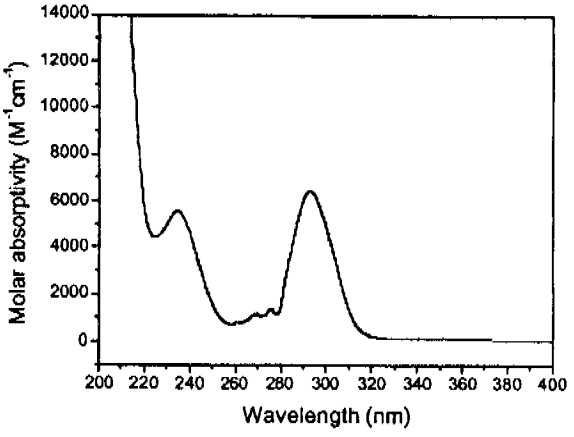


Fig. 1. Ultraviolet absorption spectrum of paroxetine in pH 7 buffered solution.

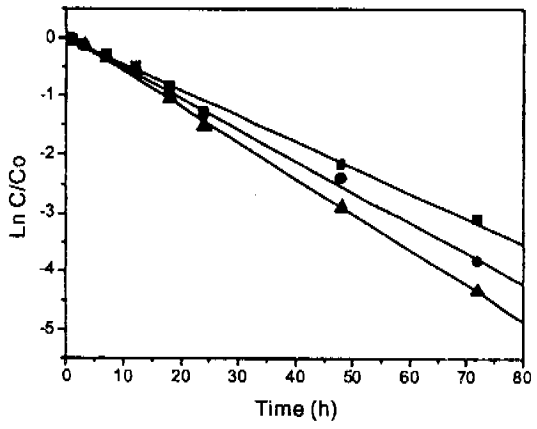


Fig. 2. Photolysis of paroxetine in three buffer solutions at 25°C. ■ = pH 5; ● = pH 7; ▲ = pH 9.

11.35 ± 0.12 h and 0.0439 ± 0.0010, 0.0529 ± 0.0016, and 0.0611 ± 0.0006 h^{-1}, respectively (Table 1). The relation coefficients (r^2) (Table 1) and the linearity of the Ln-concentration versus reaction time curves (Fig. 2) indicated that the degradation process followed first-order kinetics. The rate constants were calculated by linear regression analysis of a plot of the natural logarithm of residual paroxetine concentration versus time. These results indicated that paroxetine is more degradable under alkaline conditions than in acidic conditions by photolysis, likely via a photonucleophilic process. The quantum yields ranged from 2.71×10^{-4} to 3.77×10^{-4}. Lambropoulos et al. [10] have reported that light under wet conditions affected the degradation of paroxetine, and hydrogen peroxide was shown also to contribute to the degradation when exposed to light as well. In their experiments, photolysis in the presence of hydrogen peroxide also produced more degradation products (~18) than direct photolysis (~9).

Sensitized photodegradation of paroxetine was conducted in synthetic humic water and in two 0.2 μm–filtered lake waters. As seen in Table 1, the half-life of paroxetine in synthetic humic water (14.92 h) was a little longer than in buffered solution with the same pH (13.11 h). Also the degradation in two lake waters showed the same or slower rates than in pH buffers. These results indicate that paroxetine was not sensitive to humic material or photodegradation in aqueous solutions. The slower rate of degradation was likely due to light attenuation by natural water materials. The two photoproducts detected were consistent with those generated by the degradation of the compound when irradiated in buffer solutions. Like hydrolysis in buffer solutions, no hydrolysis was observed in synthetic humic water and lake waters in the dark. In general, humic substances are known to be sensitizers in photoreactions of organic chemicals via the generation of various active oxygen species [13–19]. These photosensitized reactions can result in accelerated photodegradation of compounds that are stable to sunlight in distilled water.

Although the rates observed in the laboratory imply rapid degradation in the environment, it is likely that this chemical would be degraded at much slower rates in true environmental situations by photodegradation, where natural organic matter in water attenuates ultraviolet light as a function of depth. When the dissipation in a natural water body due to photodegradation was simulated using the photolysis module of Exposure Analysis Modeling System at a 1-m depth using the rate constant and quantum yield data, the half-life was increased to approximately 28 y from 13 to 16 h as found in the laboratory. Although these calculations are very rough and the model outputs obviously would need to be confirmed with actual field data, they do indicate that caution should be applied when extrapolating rapid degradation rates generated under idealized laboratory conditions to field situations.

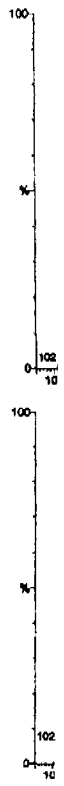
Characteristics of degradation products

The LC-ESI-MS was used to identify the structures of two photoproducts formed during photolysis of paroxetine. Photoproduct I was detected at *m/z* 210 $[M+H]^+$ (Fig. 3A), leading

Table 1. Kinetic parameters of paroxetine photodegradation in various aqueous solutions at 25°C

Media	Degradation rate (h^{-1}, avg. ± SD[a])	Half-life (h, avg. ± SD[a])	Relation coefficient (r^2)	Quantum yield (Φ, $\times 10^{-4}$)
pH 5 buffer	0.0439 ± 0.0010	15.79 ± 0.36	0.9935	2.71
pH 7 buffer	0.0529 ± 0.0016	13.11 ± 0.39	0.9981	3.26
pH 9 buffer	0.0611 ± 0.0006	11.35 ± 0.12	0.9984	3.77
SHW[b]	0.0466 ± 0.0010	14.92 ± 0.32	0.9986	—
Lake water I[c]	0.0437 ± 0.0010	15.87 ± 0.36	0.9913	—
Lake water II[d]	0.0411 ± 0.0004	16.84 ± 0.17	0.9966	—

[a] Average ± standard deviation.
[b] Synthetic humic water.
[c] From Mississippi State (MS, USA).
[d] From Ackerman (MS, USA).



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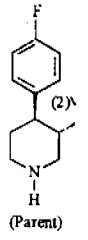

(Parent)

Fig. 4.

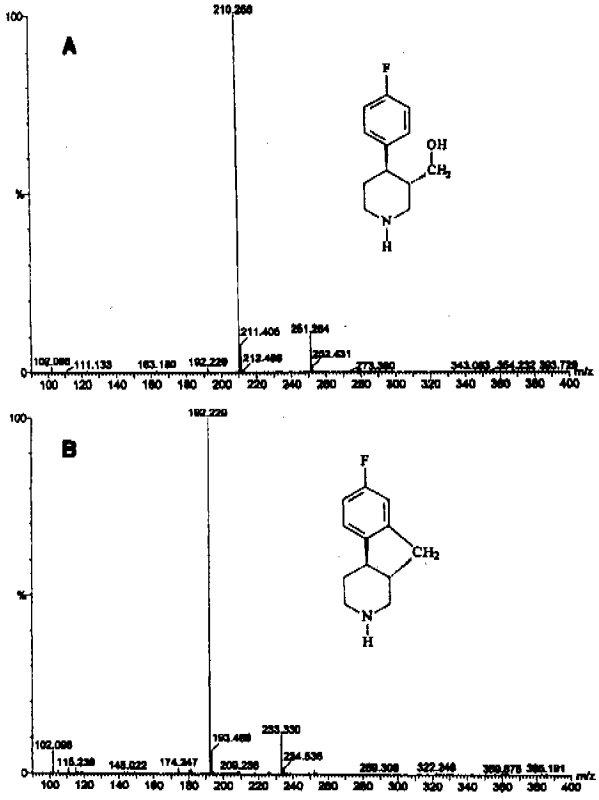

Fig. 3. The mass spectra and the chemical structures of the photoproducts I (A) and II (B).

to a molecular mass of 209. Photoproduct II was detected at *m/z* 192 $[M+H]^+$ (Fig. 3B), leading to a molecular mass of 191. As shown in Figure 3A, there was a significant adduct formation of *m/z* 251 $[M+H+CH_3CN]^+$ from *m/z* 210 $[M+H]^+$. This photoproduct appears to be formed by cleavage of the ethereal bond (cleavage of (1) in Fig. 4) of parent compound. The mass spectrum of photoproduct II also showed a significant adduct formation of *m/z* 233 $[M+H+CH_3CN]^+$ from *m/z* 192 $[M+H]^+$. It is likely that this photoproduct was produced by loss of water from photoproduct I and with subsequent cyclization (5-membered). A possible pathway for the photodegradation of paroxetine is presented in Figure 4. Two possibilities of formation to photoproduct II exist. One is transformation to photoproduct I by cleavage of (1), followed by loss of water and ring formation to photoproduct II. The other is a direct transformation to photoproduct II by cleavage of (2), followed by ring formation. Either pathway is conceivably possible. Photoproduct I was observed as an unstable intermediate, ultimately yielding photoproduct II as a stable compound, which means that photoproduct I was created as a transient intermediate in this process. The proposed reaction leading from I to II, especially cleavage of C-H bond, was clarified by Wong and Chu [26]. In their paper, an aromatic C-H bond is broken followed by hydroxylation under photolytic conditions.

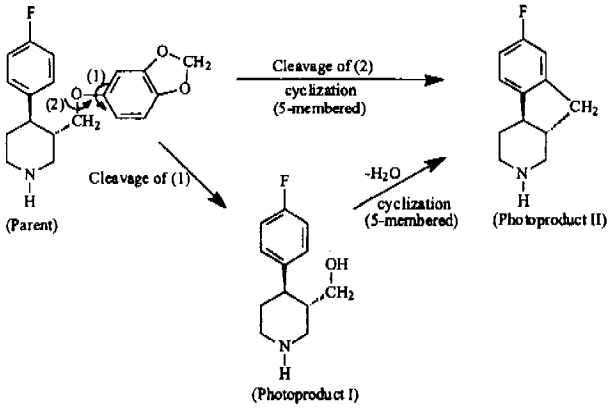

Fig. 4. A possible pathway for the photodegradation of paroxetine.

These two degradation products formed by photolysis were not consistent with metabolites found in human serum and plasma [2,3,27], however, this is not surprising because the degradation of paroxetine proceeds in each of these systems by very different mechanisms. In human serum and plasma, metabolism of paroxetine shows oxidative cleavage of the methylenedioxy bridge by cytochrome P450 (CYP) to give an unstable catechol intermediate [27]. It is methylated in the metaposition or paraposition by another enzyme other than CYP [27]. This means that the chemical degradation by photolysis is quite different from the biological one in view of the degradation patterns.

Photoproduct I was found to be unstable, with the highest amounts forming at 12 to 18 h after treatment at all pH values (Fig. 5). After this time, the amounts decreased gradually and then remained at constant levels after 72 h. However, photoproduct II increased through the experimental period of 7 d, indicating its stability to further photodegradation (Fig. 5). The stability of the two was the same in all pH buffers (Fig. 5). In a separate experiment, both photoproducts were found to be stable in irradiated solutions that were removed from the light chamber after 12 h and stored in the dark for 10 d (data not shown). This data indicates that both photoproducts appear to be hydrolytically stable and that the degradation of photoproduct I was not by hydrolysis but by photolysis completely. It is likely that the two photoproducts are more hydrophilic than the parent compound based upon retention times on the analytical column and mobile phase composition. The retention times of photoproducts were faster than that of parent compound (data not shown). When the ratio of aqueous portion of mobile phase was increased from 30 to 50%, the retention times of the two photoproducts were decreased from 4.11 to 3.23 min and from 4.65 to 3.75 min, indicating they were more soluble in water than in organic solvent (data not shown), while the retention time of parent compound was increased from 8.99 to 13.41 min at the same conditions. Using a diode array detector, the UV spectra of two photoproducts were compared with that of parent compound (Fig. 6). As shown in Figure 6, paroxetine and its photoproducts I and II exhibit quite different spectra. These UV spectra were consistent with their measured photostability. That is, photoproduct I exhibits an absorption maximum wavelength at 337 nm, which indicated that this photoproduct is susceptible to photodegradation by sunlight. In general, the maximum absorbances related to extended chromophore or n-π^* chromophore range about from 280 to 360 nm [28]. However, there is a paper that amlodipine has a similar chemical structure to photoproduct I and a maximum wavelength at around 360 nm [29]. Photoproduct II, however, does not absorb light at wavelengths above 280 nm. This means that it can be stable to sunlight under direct photolysis.

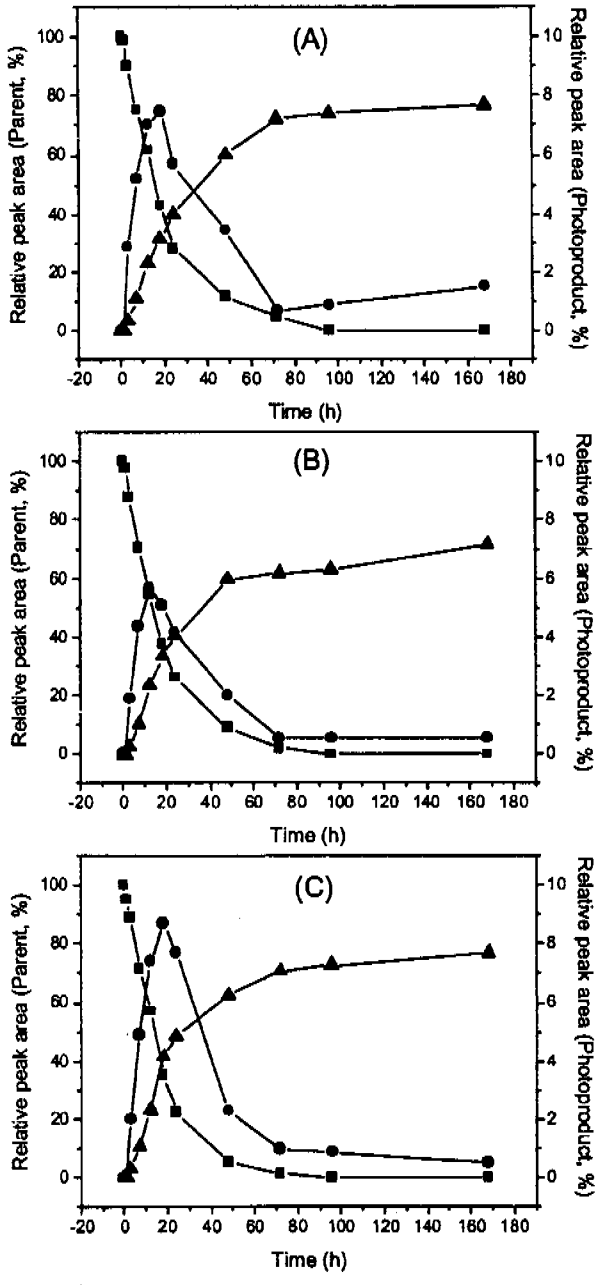

Fig. 5. Change in parent compound (■), photoproduct I (●), and II (▲) during the photolysis in buffer solutions. pH 5 (**A**); pH 7 (**B**); pH 9 (**C**).

CONCLUSION

Paroxetine was shown to be stable under dark conditions in solutions for at least 30 d, yet was found to be degraded rapidly by simulated sunlight in the laboratory. The two photodegradation products detected were observed in buffered distilled water as well as in natural water. Photoproduct I was degraded by photolysis, while photoproduct II was stable and accumulated after it was formed. As mentioned earlier, the proposed structures are based upon direct interpretation of mass spectral data and chromatographic behavior. Comparison of the spectral and chromatographic data with that generated from authentic synthesized standards would be necessary for absolute confirmation of these structures.

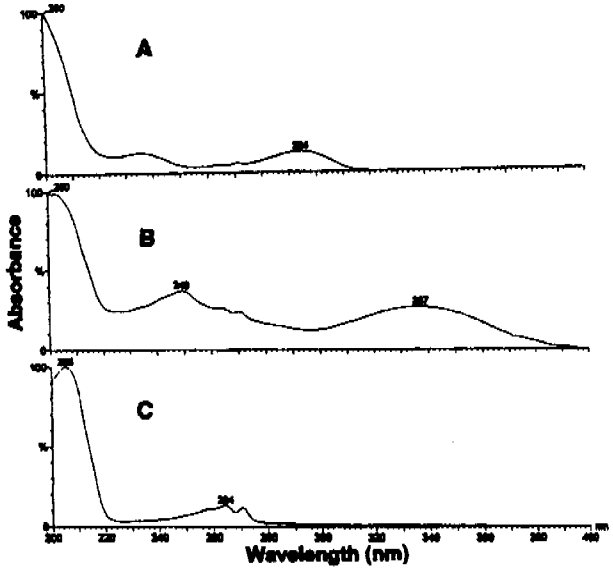

Fig. 6. Ultraviolet absorption spectra of paroxetine (**A**), photoproduct I (**B**), and photoproduct II (**C**), recorded by photo diode array detector.

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REFERENCES

1. Fong PP. 1998. Zebra mussel spawning is induced in low concentrations of putative serotonin selective reuptake inhibitors. *Biol Bull* 194:143–149.
2. Haddock RE, Johnson AM, Langley PF. 1989. Metabolic pathway of paroxetine in animals and man and the comparative pharmacological properties of its metabolites. *Acta Psychiatr Scand* 80: 24–28.
3. Kaye CM, Haddock RE, Langley PF. 1989. A review of the metabolism and pharmacokinetics of paroxetine in man. *Acta Psychiatr Scand* 80:60–75.
4. Shin JG, Kim KA, Yoon YR, Cha IJ, Kim YH, Shin SG. 1998. Rapid simple high-performance chromatographic determination of paroxetine in human plasma. *J Chromatogr B* 713:45–456.
5. Knoeller J, Vogt-schenken R, Brett MA. 1995. A simple and robust HPLC method for the determination of paroxetine in human plasma. *J Pharm Biomed Anal* 13:635–638.
6. Foglia JP, Sorisio D, Kirshner M, Pollock BG. 1997. Quantitative determination of paroxetine in plasma by high-performance liquid chromatography and ultraviolet detection. *J Chromatogr B* 693: 147–151.
7. Lucca A, Gentilini G, Lopez-Silva S, Soldarini A. 2000. Simultaneous determination of human plasma levels of four selective serotonin reuptake inhibitors by high-performance liquid chromatography. *Ther Drug Monit* 22:271–276.
8. Lacassie E, Gaulier JM, Marquet P, Rabatel JF, Lachâtre G. 2000. Methods for the determination of seven selective serotonin reuptake inhibitors and three active metabolites in human serum using high-performance chromatography and gas chromatography. *J Chromatogr B* 742:229–238.
9. Gupta RN. 1994. Column liquid chromatographic determination of paroxetine in human serum using solid-phase extraction. *J Chromatogr B* 661:362–365.
10. Lambropoulos J, Spanos GA, Lazaridis NV. 1999. Method development and validation for the HPLC assay (potency and related substances) for 20 mg patoxetine tablets. *J Pharm Biomed Anal* 19:793–802.
11. Skibiński R, Misztal G. 2001. Determination of moclobemide, paroxetine, and fluvoxamine in tablets by HPLC. *Acta Pol Pharma Drug Research* 58:97–100.
12. Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, Barber LB, Buxton HT. 2002. Pharmaceuticals, hormones, and

other organic wastewater contaminants in U.S. streams, 1999–2000: A national reconnaissance. *Environ Sci Technol* 36:1202–1211.
13. Zepp RG, Schlotzhauer PF, Sink RM. 1985. Photosensitized transformations involving electronic energy transfer in natural waters: Role of humic substances. *Environ Sci Technol* 19:74–81.
14. Fukushima M, Tatsumi K, Morimoto K. 2000. Influence of iron(III) and humic acid on the photodegradation of pentachlorophenol. *Environ Toxicol Chem* 19:1711–1716.
15. Keum YS, Kim JH, Kim YH, Kim K, Li QX. 2002. Photodegradation of diafenthiuron in water. *Pest Manag Sci* 58:496–502.
16. Voelker BM, Morel FM, Sulzberger B. 1997. Iron redox cycling in surface waters: Effect of humic substances and light. *Environ Sci Technol* 31:1004–1011.
17. Aguer JP, Richard C. 1996. Reactive species produced on irradation at 365 nm of aqueous solutions of humic acids. *J Photochem Photobiol A* 93:193–198.
18. Fukushima M, Tatsumi K. 1998. Light acceleration of iron(III) reduction by humic acid in the aqueous solution. *Colloids Surf A Physicochem Engineer Aspects* 155:249–258.
19. Zepp RG, Braun AM, Hoigné J, Leenheer JA. 1987. Photoproduction of hydrated electron from natural organic solutes in aquatic environments. *Environ Sci Technol* 21:485–490.
20. Draper W, Crosby DG. 1981. Hydrogen peroxide and hydroxyl radical: Intermediates in indirect photolysis reactions in water. *J Agric Food Chem* 29:699–702.
21. Moffett JW, Zika RG. 1987. Reaction kinetics of hydrogen peroxide with copper and iron in seawater. *Environ Sci Technol* 21: 804–810.
22. Armbrust KL. 1999. Photochemical process influencing pesticide degradation in rice paddies. *J Pestic Sci* 24:69–73.
23. Vaughan PP, Blough NV. 1998. Photochemical formation of hydroxyl radical by constituents of natural waters. *Environ Sci Technol* 32:2947–2953.
24. Mabury SA, Crosby DG. 1996. Pesticide reactivity toward hydroxyl and its relationship to field persistence. *J Agric Food Chem* 44:1920–1924.
25. U.S. Environmental Protection Agency. 1998. Fate, transport, and transformation test guidelines—OPPTS 835.5270, Indirect photolysis screening test. EPA/712-C-98-099. Washington, DC.
26. Wong CC, Chu W. 2003. The hydrogen peroxide–assisted photocatalytic degradation of alachlor in TiO_2 suspensions. *Environ Sci Technol* 37:2310–2316.
27. Hemeryck A, Belpaire FM. 2002. Selective serotonin reuptake inhibitors and cytochrome P450-mediated drug–drug interactions: An uptake. *Curr Drug Metab* 3:13–37.
28. Silverstein RM, Bassler GC, Morril TC. 1991. *Spectrometric Identification of Organic Compounds*, 15th ed. John Wiley, New York, NY, USA.
29. Ragno G, Garofalo A, Vetuschi C. 2002. Photodegradation monitoring of amlodipine by derivative spctrophotometry. *J Pharm Biomed Anal* 27:19–24.